\_\_\_\_\_\_

Sequence Listing was accepted.

See attached Validation Report.

If you need help call the Patent Electronic Business Center at (866)

217-9197 (toll free).

Reviewer: Anne Corrigan

Timestamp: [year=2009; month=10; day=8; hr=13; min=58; sec=10; ms=541; ]

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## Validated By CRFValidator v 1.0.3

Application No: 10576281 Version No: 1.0

Input Set:

Output Set:

**Started:** 2009-10-08 11:07:58.734 **Finished:** 2009-10-08 11:07:59.492

Artificial or Unknown found in <213> in SEQ ID (21)

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Total Warnings: 1

Total Errors: 1

No. of SeqIDs Defined: 21

213

Actual SeqID Count: 21

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## SEQUENCE LISTING

| <110>   | Toshihiro NAKAJIMA Tetsuya AMANO Lei ZHANG Rie IKEDA Satoshi YAMASAKI Naoko YAGISHITA                              |     |
|---------|--------------------------------------------------------------------------------------------------------------------|-----|
| <120>   | Method of inhibiting secretase activity                                                                            |     |
| <130>   | L7350.0007                                                                                                         |     |
| <140>   | 10576281                                                                                                           |     |
| <141>   | 2009-10-08                                                                                                         |     |
| <150>   | PCT/JP2004/015950                                                                                                  |     |
| <151>   | 2004-10-20                                                                                                         |     |
| <150>   | JP2003-359704                                                                                                      |     |
|         | 2003-10-20                                                                                                         |     |
| <160>   | 21                                                                                                                 |     |
| <170>   | PatentIn version 3.4                                                                                               |     |
| <210>   | 1                                                                                                                  |     |
| <211>   | 3374                                                                                                               |     |
| <212>   | DNA                                                                                                                |     |
| <213>   | Homo sapiens                                                                                                       |     |
|         |                                                                                                                    |     |
| <220>   |                                                                                                                    |     |
| <221>   | CDS                                                                                                                |     |
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|         | -<br>tctt atgagcatgc ctgtgttggg ttgacagtga gggtaataat gacttgttgg                                                   | 60  |
|         |                                                                                                                    |     |
| ttgatt  | gtag atatagggct ctcccttgca aggtaattag gctccttaaa ttacctgtaa                                                        | 120 |
| gatttt  | cttg ccacagcatc cattctggtt aggctggtga tcttctgagt agtgatagat                                                        | 180 |
| tggttg  | gtgg tgaggtttac aggtgttccc ttctcttact cctggtgttg gctacaatca                                                        | 240 |
| ggtggc  | gtet agageageat gggacaggtg ggtaagggga gtetteteat tatgeagaag                                                        | 300 |
| tgatca  | actt aaatetetgt cagatetace tttatgtage eeggeagteg egeggattga                                                        | 360 |
| gcgggct | tege ggegetgggt teetggtete egggeeaggg ea atg tte ege aeg<br>Met Phe Arg Thr<br>1                                   | 414 |
|         | g atg atg gcg gcc agc ctg gcg ctg acc ggg gct gtg gct<br>l Met Met Ala Ala Ser Leu Ala Leu Thr Gly Ala Val Val Ala | 462 |

|                                 | -                                      |                                                      |                                         |                                               |                                               |                                        | _                                                    | ttc<br>Phe                      |                                                      |                                 |                                                      |                                        | -                                             |                                               | _                                             | 510        |
|---------------------------------|----------------------------------------|------------------------------------------------------|-----------------------------------------|-----------------------------------------------|-----------------------------------------------|----------------------------------------|------------------------------------------------------|---------------------------------|------------------------------------------------------|---------------------------------|------------------------------------------------------|----------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|------------|
|                                 | _                                      |                                                      | _                                       |                                               | -                                             | _                                      | -                                                    | gtc<br>Val<br>45                | _                                                    |                                 |                                                      | _                                      | -                                             |                                               | _                                             | 558        |
|                                 | _                                      |                                                      |                                         | _                                             |                                               | _                                      |                                                      | atg<br>Met                      |                                                      | _                               |                                                      |                                        |                                               |                                               |                                               | 606        |
| _                               |                                        | -                                                    | -                                       |                                               | _                                             |                                        |                                                      | ctt<br>Leu                      | _                                                    | _                               | -                                                    |                                        |                                               |                                               | _                                             | 654        |
| _                               |                                        |                                                      |                                         | _                                             | _                                             | _                                      |                                                      | acc<br>Thr                      | _                                                    |                                 |                                                      | _                                      | -                                             |                                               | _                                             | 702        |
|                                 | _                                      |                                                      | _                                       | -                                             |                                               |                                        |                                                      | ctt<br>Leu                      |                                                      |                                 |                                                      |                                        |                                               | _                                             |                                               | 750        |
|                                 |                                        | _                                                    | -                                       |                                               | -                                             | -                                      |                                                      | gac<br>Asp<br>125               |                                                      | _                               | _                                                    | _                                      | _                                             |                                               |                                               | 798        |
|                                 |                                        |                                                      |                                         |                                               |                                               | _                                      | _                                                    | att<br>Ile                      | -                                                    |                                 |                                                      | _                                      |                                               |                                               | _                                             | 846        |
|                                 |                                        | 135                                                  |                                         |                                               |                                               |                                        | 140                                                  |                                 |                                                      |                                 |                                                      |                                        |                                               |                                               |                                               |            |
|                                 |                                        | ctg                                                  | -                                       |                                               |                                               |                                        | gtc                                                  | agc<br>Ser                      |                                                      | -                               |                                                      |                                        | _                                             |                                               | _                                             | 894        |
| Gly                             | Ile<br>150<br>cgt                      | ctg<br>Leu<br>ggg                                    | Asp                                     | Phe<br>tct                                    | Leu<br>gtg                                    | Phe<br>155<br>cag                      | gtc<br>Val<br>ctg                                    | _                               | His<br>ttt                                           | Ala                             | Tyr<br>160<br>ttt                                    | His<br>gag                             | Ser                                           | Ile<br>gcc                                    | Leu                                           | 894<br>942 |
| Gly acc Thr 165                 | Ile<br>150<br>cgt<br>Arg               | ctg<br>Leu<br>ggg<br>Gly                             | Asp<br>gcc<br>Ala                       | Phe<br>tct<br>Ser                             | Leu<br>gtg<br>Val<br>170                      | Phe<br>155<br>cag<br>Gln               | gtc<br>Val<br>ctg<br>Leu                             | Ser                             | His<br>ttt<br>Phe                                    | Ala<br>ggc<br>Gly<br>175        | Tyr<br>160<br>ttt<br>Phe                             | His<br>gag<br>Glu<br>gtg               | Ser<br>tat<br>Tyr                             | Ile<br>gcc<br>Ala                             | Leu atc Ile 180                               |            |
| Gly acc Thr 165 ctg Leu         | cgt<br>Arg<br>atg<br>Met               | ctg<br>Leu<br>ggg<br>Gly<br>acg<br>Thr               | Asp<br>gcc<br>Ala<br>atg<br>Met         | tct<br>Ser<br>gtg<br>Val<br>185               | gtg<br>Val<br>170<br>ctc<br>Leu               | Phe<br>155<br>cag<br>Gln<br>acc<br>Thr | gtc<br>Val<br>ctg<br>Leu<br>atc<br>Ile               | Ser<br>gtg<br>Val               | ttt<br>Phe<br>atc<br>Ile<br>190                      | Ala ggc Gly 175 aag Lys         | Tyr<br>160<br>ttt<br>Phe<br>tat<br>Tyr               | His<br>gag<br>Glu<br>gtg<br>Val        | Ser tat Tyr ctg Leu                           | gcc<br>Ala<br>cac<br>His<br>195               | atc<br>Ile<br>180<br>tcc<br>Ser               | 942        |
| Gly acc Thr 165 ctg Leu gtg Val | Ile<br>150<br>cgt<br>Arg<br>atg<br>Met | ctg<br>Leu<br>ggg<br>Gly<br>acg<br>Thr<br>ctc<br>Leu | Asp  gcc Ala  atg Met  cag Gln 200  gag | tct<br>ser<br>gtg<br>Val<br>185<br>agt<br>ser | gtg<br>Val<br>170<br>ctc<br>Leu<br>gag<br>Glu | Phe<br>155<br>cag<br>Gln<br>acc<br>Thr | gtc<br>Val<br>ctg<br>Leu<br>atc<br>Ile<br>ccc<br>Pro | ser<br>gtg<br>Val<br>ttc<br>Phe | His<br>ttt<br>Phe<br>atc<br>Ile<br>190<br>gac<br>Asp | Ala ggc Gly 175 aag Lys aac Asn | Tyr<br>160<br>ttt<br>Phe<br>tat<br>Tyr<br>aag<br>Lys | gag<br>Glu<br>gtg<br>Val<br>gct<br>Ala | tat<br>Tyr<br>ctg<br>Leu<br>gtg<br>Val<br>210 | gcc<br>Ala<br>cac<br>His<br>195<br>tac<br>Tyr | atc<br>Ile<br>180<br>tcc<br>Ser<br>atg<br>Met | 942<br>990 |

|     |     |     | _   |     | _   | -   | _   | _   |     |     | _   |     | -   | gtg<br>Val        |     | 1182 |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------------------|-----|------|
| _   | _   |     | _   |     | _   | _   | _   |     | _   |     | _   |     |     | ctg<br>Leu<br>275 |     | 1230 |
|     | _   | _   |     |     |     |     |     | _   | _   | _   | _   |     | -   | tgc<br>Cys        |     | 1278 |
|     | _   | _   | _   |     | _   |     |     |     | _   | _   | _   | _   |     | tgc<br>Cys        |     | 1326 |
|     |     |     |     |     | _   | _   | _   | _   |     |     |     | _   |     | cag<br>Gln        | _   | 1374 |
|     | _   |     |     | _   | _   | _   | -   | _   |     | _   | _   | _   | _   | cca<br>Pro        |     | 1422 |
| _   |     |     |     |     | _   |     |     |     | _   |     |     |     |     | cct<br>Pro<br>355 | _   | 1470 |
|     |     |     |     |     |     | _   |     |     |     |     |     |     |     | cag<br>Gln        |     | 1518 |
|     | _   |     |     |     |     |     |     | _   |     |     | _   |     |     | ccc<br>Pro        | _   | 1566 |
|     |     |     |     |     | -   | _   |     |     |     | _   |     |     |     | gct<br>Ala        |     | 1614 |
| _   |     |     |     |     | -   | -   | -   | -   |     |     |     |     | -   | gga<br>Gly        | _   | 1662 |
| -   |     |     |     | -   | -   |     |     | _   | -   |     | -   | -   |     | gcc<br>Ala<br>435 |     | 1710 |
| _   |     |     |     |     |     |     |     | _   |     |     | _   |     |     | gcc<br>Ala        |     | 1758 |
|     |     |     |     |     |     |     |     | _   |     | _   |     | _   |     | cca<br>Pro        |     | 1806 |
| ttt | gcc | ttc | ccc | cca | atg | cct | gtg | ccc | cct | gcg | ggc | ttt | gct | ggg               | ctg | 1854 |

| Phe Ala Phe Pro Pro Met Pro Val Pro Pro Ala Gly Phe Ala Gly Leu 470 475 480                                                                       |      |
|---------------------------------------------------------------------------------------------------------------------------------------------------|------|
| acc cca gag gag cta cga gct ctg gag ggc cat gag cgg cag cac ctg Thr Pro Glu Glu Leu Arg Ala Leu Glu Gly His Glu Arg Gln His Leu 485 490 495 500   | 1902 |
| gag gcc cgg ctg cag agc ctg cgt aac atc cac aca ctg ctg gac gcc Glu Ala Arg Leu Gln Ser Leu Arg Asn Ile His Thr Leu Leu Asp Ala 505 510 515       | 1950 |
| gcc atg ctg cag atc aac cag tac ctc acc gtg ctg gcc tcc ttg ggg Ala Met Leu Gln Ile Asn Gln Tyr Leu Thr Val Leu Ala Ser Leu Gly 520 525 530       | 1998 |
| cccccccggcctgccacttcagtcacttccactgaggggactgccactProProArgProAlaThrSerValAsnSerThrGluGlyThrAlaThr535540545                                         | 2046 |
| aca gtt gtt gct gct gcc tcc tcc acc agc atc cct agc tca gag gcc Thr Val Val Ala Ala Ala Ser Ser Thr Ser Ile Pro Ser Ser Glu Ala 550 555 560       | 2094 |
| acg acc cca acc cca gga gcc tcc cca cca gcc cct gaa atg gaa agg Thr Thr Pro Thr Pro Gly Ala Ser Pro Pro Ala Pro Glu Met Glu Arg 565 570 575 580   | 2142 |
| cct cca gct cct gag tca gtg ggc aca gag gag atg cct gag gat gga<br>Pro Pro Ala Pro Glu Ser Val Gly Thr Glu Glu Met Pro Glu Asp Gly<br>585 590 595 | 2190 |
| gag ccc gat gca gca gag ctc cgc cgg cgc cgc ctg cag aag ctg gag Glu Pro Asp Ala Ala Glu Leu Arg Arg Arg Arg Leu Gln Lys Leu Glu 600 605 610       | 2238 |
| tct cct gtt gcc cac tga cactgcccca gcccagcccc agcctctgct<br>Ser Pro Val Ala His<br>615                                                            | 2286 |
| cttttgagea geeetegetg gaacatgtee tgeeaceaag tgeeagetee etetetgtet                                                                                 | 2346 |
| gcaccaggga gtagtacccc cagctctgag aaagaggcgg catcccctag gccaagtgga                                                                                 | 2406 |
| aagaggetgg ggtteeeatt tgaeteeagt eeeaggeage eatggggate tegggteagt                                                                                 | 2466 |
| tccagccttc ctctccaact cttcagccct gtgttctgct ggggccatga aggcagaagg                                                                                 | 2526 |
| tttagcctct gagaagccct cttcttcccc caccctttc caggagaagg ggctgcccct                                                                                  | 2586 |
| ccaagcccta cttgtatgtg cggagtcaca ctgcagtgcc gaacagtatt agctcccgtt                                                                                 | 2646 |
| cccaagtgtg gactccagag gggctggagg caagctatga acttgctcgc tggcccaccc                                                                                 | 2706 |
| ctaagactgg tacccattte ettttettae eetgatetee eeagaageet ettgtggtgg                                                                                 | 2766 |
| tggctgtgcc ccctatgccc tgtggcattt ctgcgtctta ctggcaacca cacaactcag                                                                                 | 2826 |

| ggaaaggaat | gcctgggagt | gggggtgcag | gcgggcagca | ctgagggacc | ctgccccgcc | 2886 |
|------------|------------|------------|------------|------------|------------|------|
| cctccccca  | ggcccctttc | ccctgcagct | tctcaagtga | gactgacctg | tctcacccag | 2946 |
| cagccactgc | ccagccgcac | tccaggcaag | ggccagtgcg | cctgctcctg | accactgcaa | 3006 |
| tcccagcgcc | caaggaaggc | cacttctcaa | ctggcagaac | ttctgaagtt | tagaattgga | 3066 |
| attacttcct | tactagtgtc | ttttggctta | aattttgtct | tttgaagttg | aatgcttaat | 3126 |
| cccgggaaag | aggaacagga | gtgccagact | cctggtcttt | ccagtttaga | aaaggctctg | 3186 |
|            | ggaccacagg |            |            |            |            | 3246 |
|            | agttgttgga |            |            |            |            | 3306 |
|            | gcttaaattg | tatatacagc | caaataaaaa | cttgcattaa | caaaaaaaa  | 3366 |
| aaaaaaa    |            |            |            |            |            | 3374 |

<210> 2

<211> 617

<212> PRT

<213> Homo sapiens

<400> 2

Met Phe Arg Thr Ala Val Met Met Ala Ala Ser Leu Ala Leu Thr Gly

1 5 10 15

Ala Val Val Ala His Ala Tyr Tyr Leu Lys His Gln Phe Tyr Pro Thr 20 25 30

Val Val Tyr Leu Thr Lys Ser Ser Pro Ser Met Ala Val Leu Tyr Ile  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45 \hspace{1.5cm}$ 

Gln Ala Phe Val Leu Val Phe Leu Leu Gly Lys Val Met Gly Lys Val
50 55 60

Phe Phe Gly Gln Leu Arg Ala Ala Glu Met Glu His Leu Leu Glu Arg 65 70 75 80

Ser Trp Tyr Ala Val Thr Glu Thr Cys Leu Ala Phe Thr Val Phe Arg 85 90 95

Asp Asp Phe Ser Pro Arg Phe Val Ala Leu Phe Thr Leu Leu Leu Phe 100 105 110

Leu Lys Cys Phe His Trp Leu Ala Glu Asp Arg Val Asp Phe Met Glu

115 120 125

Arg Ser Pro Asn Ile Ser Trp Leu Phe His Cys Arg Ile Val Ser Leu 130 135 140 Met Phe Leu Leu Gly Ile Leu Asp Phe Leu Phe Val Ser His Ala Tyr 150 155 His Ser Ile Leu Thr Arg Gly Ala Ser Val Gln Leu Val Phe Gly Phe 165 170 Glu Tyr Ala Ile Leu Met Thr Met Val Leu Thr Ile Phe Ile Lys Tyr 180 185 190 Val Leu His Ser Val Asp Leu Gln Ser Glu Asn Pro Trp Asp Asn Lys 195 200 205 Ala Val Tyr Met Leu Tyr Thr Glu Leu Phe Thr Gly Phe Ile Lys Val 210 215 220 Leu Leu Tyr Met Ala Phe Met Thr Ile Met Ile Lys Val His Thr Phe 225 230 235 240 Pro Leu Phe Ala Ile Arg Pro Met Tyr Leu Ala Met Arg Gln Phe Lys 250 255 245 Lys Ala Val Thr Asp Ala Ile Met Ser Arg Arg Ala Ile Arg Asn Met 265 260 270 Asn Thr Leu Tyr Pro Asp Ala Thr Pro Glu Glu Leu Gln Ala Met Asp 275 280 285 Asn Val Cys Ile Ile Cys Arg Glu Glu Met Val Thr Gly Ala Lys Arg 295 290 Leu Pro Cys Asn His Ile Phe His Thr Ser Cys Leu Arg Ser Trp Phe 305 310 315 320 Gln Arg Gln Gln Thr Cys Pro Thr Cys Arg Met Asp Val Leu Arg Ala 330 325

Ser Leu Pro Ala Gln Ser Pro Pro Pro Glu Pro Ala Asp Gln Gly

345

350

340

| Pro        | Pro        | Pro<br>355 | Ala        | Pro        | His        | Pro        | Pro<br>360 | Pro        | Leu        | Leu        | Pro        | Gln<br>365 | Pro        | Pro        | Asn        |  |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|--|
| Phe        | Pro<br>370 | Gln        | Gly        | Leu        | Leu        | Pro<br>375 | Pro        | Phe        | Pro        | Pro        | Gly<br>380 | Met        | Phe        | Pro        | Leu        |  |
| Trp<br>385 | Pro        | Pro        | Met        | Gly        | Pro<br>390 | Phe        | Pro        | Pro        | Val        | Pro<br>395 | Pro        | Pro        | Pro        | Ser        | Ser<br>400 |  |
| Gly        | Glu        | Ala        | Val        | Ala<br>405 | Pro        | Pro        | Ser        | Thr        | Ser<br>410 | Ala        | Ala        | Ala        | Leu        | Ser<br>415 | Arg        |  |
| Pro        | Ser        | Gly        | Ala<br>420 | Ala        | Thr        | Thr        | Thr        | Ala<br>425 | Ala        | Gly        | Thr        | Ser        | Ala<br>430 | Thr        | Ala        |  |
| Ala        | Ser        | Ala<br>435 | Thr        | Ala        | Ser        | Gly        | Pro<br>440 | Gly        | Ser        | Gly        | Ser        | Ala<br>445 | Pro        | Glu        | Ala        |  |
| Gly        | Pro<br>450 | Ala        | Pro        | Gly        | Phe        | Pro<br>455 | Phe        | Pro        | Pro        | Pro        | Trp<br>460 | Met        | Gly        | Met        | Pro        |  |
| Leu<br>465 | Pro        | Pro        | Pro        | Phe        | Ala<br>470 | Phe        | Pro        | Pro        | Met        | Pro<br>475 | Val        | Pro        | Pro        | Ala        | Gly<br>480 |  |
| Phe        | Ala        | Gly        | Leu        | Thr<br>485 | Pro        | Glu        | Glu        | Leu        | Arg<br>490 | Ala        | Leu        | Glu        | Gly        | His<br>495 | Glu        |  |
| Arg        | Gln        | His        | Leu<br>500 | Glu        | Ala        | Arg        | Leu        | Gln<br>505 | Ser        | Leu        | Arg        | Asn        | Ile<br>510 | His        | Thr        |  |
| Leu        | Leu        | Asp<br>515 | Ala        | Ala        | Met        | Leu        | Gln<br>520 | Ile        | Asn        | Gln        | Tyr        | Leu<br>525 | Thr        | Val        | Leu        |  |
| Ala        | Ser<br>530 | Leu        | Gly        | Pro        | Pro        | Arg<br>535 | Pro        | Ala        | Thr        | Ser        | Val<br>540 | Asn        | Ser        | Thr        | Glu        |  |
| Gly<br>545 | Thr        | Ala        | Thr        | Thr        | Val<br>550 | Val        | Ala        | Ala        | Ala        | Ser<br>555 | Ser        | Thr        | Ser        | Ile        | Pro<br>560 |  |
| Ser        | Ser        | Glu        | Ala        | Thr        | Thr        | Pro        | Thr        | Pro        | Gly        | Ala        | Ser        | Pro        | Pro        | Ala        | Pro        |  |

|                |         | 580   |       |       |     |     | 585 |     |     | 2   |     | 590 |     |     |     |
|----------------|---------|-------|-------|-------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                |         |       |       |       |     |     |     |     |     |     |     |     |     |     |     |
|                | _       |       |       | _     | _   |     |     |     | _   |     | _   | _   | _   |     |     |
| Pro Gl         |         | Gly   | Glu   | Pro   | Asp |     | Ala | Glu | Leu | Arg |     | Arg | Arg | Leu |     |
|                | 595     |       |       |       |     | 600 |     |     |     |     | 605 |     |     |     |     |
|                |         |       |       |       |     |     |     |     |     |     |     |     |     |     |     |
| Gln Ly         | s Leu   | Glu   | Ser   | Pro   | Val | Ala | His |     |     |     |     |     |     |     |     |
| 61             |         |       |       |       | 615 |     |     |     |     |     |     |     |     |     |     |
|                |         |       |       |       |     |     |     |     |     |     |     |     |     |     |     |
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| <212>          | DNA     |       |       |       |     |     |     |     |     |     |     |     |     |     |     |
| <213>          | Homo    | sap:  | lens  |       |     |     |     |     |     |     |     |     |     |     |     |
| <400>          | 3       |       |       |       |     |     |     |     |     |     |     |     |     |     |     |
| aatgtc         |         | tcato | ctaco | co a  | ra  |     |     |     |     |     |     |     |     |     | 23  |
| <b>3</b>       | - 9     |       | 5-    | - 5   | J   |     |     |     |     |     |     |     |     |     |     |
|                |         |       |       |       |     |     |     |     |     |     |     |     |     |     |     |
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| <213>          | Homo    | sap:  | iens  |       |     |     |     |     |     |     |     |     |     |     |     |
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|                |         |       |       |       |     |     |     |     |     |     |     |     |     |     |     |
| .010.          | 6       |       |       |       |     |     |     |     |     |     |     |     |     |     |     |
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|                |         |       |       |       |     |     |     |     |     |     |     |     |     |     |     |
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| <210>          | 7       |       |       |       |     |     |     |     |     |     |     |     |     |     |     |
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| <212><br><213> | DNA     | g 25. | iena  |       |     |     |     |     |     |     |     |     |     |     |     |
| \Z13\          | Homo    | sap.  | rens  |       |     |     |     |     |     |     |     |     |     |     |     |
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| aaggtt         |         | tgtad | catgo | gc ct | :t  |     |     |     |     |     |     |     |     |     | 23  |
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Glu Met Glu Arg Pro Pro Ala Pro Glu Ser Val Gly Thr Glu Glu Met

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